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ORIGINAL ARTICLE

Quantitative structure–activity relationship based modeling of substituted indole Schiff bases as inhibitor of COX-2

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Abstract We have performed the quantitative structure activity relationship (QSAR) study for N-1 and C-3 substituted indole shiff bases to understand the structural features that influence the inhibitory activity toward the cyclooxygenase-2 (COX-2) enzyme. The calculated QSAR results revealed that the drug activity could be modeled by using molecular connectivity indices ($^{0}\chi$, $^{1}\chi$, $^{2}\chi$), wiener index (W) and mean wiener index (WA) parameters. The predictive ability of models was cross validated by evaluating the low residual activity, appreciable cross validated r^2 values (R^2_{cv}) and leave one out (LOO) technique.

1. Introduction

The non-steroidal anti-inflammatory drugs (NSAIDs) like aspirin are among the most common medications in the world (Vane, 1971). The mechanism of action of these drugs is the inhibition of the cyclooxygenase (COX) enzyme, which catalyzes the first step of the biosynthesis of PGG2 from arachidonic acid to generate prostaglandin H2 (Hamberg and Samuelsson, 1973). The next hierarchical step in enzyme catalysis is to convert prostaglandin H2 to other prostaglandins and thromboxanes and finally bind to G-protein-coupled receptors and effect diverse biological responses (Funk, 2001).

On the basis of crystal structures, the two isoforms (COX-1 and COX-2) have been identified. Cyclooxygenase-1 (COX-1) which is mainly associated with prostaglandin production in gastric mucosa and thromboxane production in platelets (Smith et al., 2000) and COX-2 whose expression is upregulated in response to inflammatory stimuli and elevates prostaglandin levels as part of the inflammatory response. Identification of this alternate role of COX-2 has led to development of the COX-2 selective NSAIDs such as rofecoxib, celecoxib, and valdecoxib. These drugs have good anti-inflammatory activity, but with reduced ulcerogenicity compared to nonselective NSAIDs. Despite their commercial success, current COX-2 selective inhibitors may still exhibit undesirable side effects, including the increased risk of adverse thromboembolytic events in susceptible individuals (Solomon et al., 2002; FitzGerald, 2004). Enzyme specificity is also an issue, as the sulfonamide containing inhibitors celecoxib and valdecoxib can also inhibit carbonic anhydrase II (Klebe et al., 2004).

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COX-1 selective inhibitors also have therapeutic value, as it was shown recently that COX-1 is over expressed in some ovarian cancer cells, where it stimulates angiogenesis (Gupta et al., 2003). Thus, a more detailed understanding of COX isoform differences could aid in the design of more selective, and potent, inhibitors of both COX isoforms. Both COX-1 and COX-2 are isomorphs however, the selectivity of COX-2 over COX-1 is due to the central channel of COX-2 which is larger (~17%) than that of COX-1. This difference in size is due to the change of some amino acid residues that increase the size and change the chemical environment of the binding pocket of NSAIDs. The most critical structural feature conferring sensitivity to inhibition by COX-2 is the exchange of valine in COX-2 at positions 434 and 523 in place of isoleucine in COX-1. (It is important to note that the residues in COX-2 are given the same number as their equivalent amino acids in COX-1 for convenience; however, the exact amino acid residue number in COX-2 should be calculated by subtracting 14 from the COX-1 number) (Luong et al., 1996; Iyashiro and Penning et al., 1996; Copeland et al., 1994). Also in COX-2, 17th amino acids are absent from the N terminus and 18th amino acids are inserted at the C terminus in comparison to COX-1. (Otto and Smith, 1995; Herschman, 1996).

The COX-2 enzyme is the inducible isoform that is produced by various cell types

upon exposure to cytokines, mitogens, and endotoxins released during injury and therefore molecules that inhibit its enzymatic activity would be of therapeutic value (Smith and Dewitt, 1996) The gastrointestinal side effects associated with NSAIDs are due to the inhibition of gastroprotective PGs synthesized through the COX-1 pathway. Thus, selective inhibition of COX-2 over COX-1 is considered to be highly useful for the treatment of inflammation and inflammation associated disorders with reduced gastrointestinal toxicities when compared with NSAIDs (Meade et al., 1993).

The present work aims to develop the understanding toward the inhibition of COX-2 with the help of QSAR. For this purpose we have taken the activity data (IC_{50}) that were reported by Kaur et al. (2012). The physicochemical properties of a drug play a major role in the development of formulation and bioavailability and thus we have taken some physicochemical parameters like molecular connectivity indices ($^0\chi$, $^1\chi$, $^2\chi$) with wiener index (W) as, mean wiener index (W_A), and molecular weight (MW) for the present article.

2. Experimental section

2.1. Methodology

Inhibitory activity as reported by Kaur et al. (2012) as IC_{50} were converted into their log units (log IC_{50}) and used in the present investigation. An attempt has been made to correlate the activity of these compounds with various physicochemical parameters such as surface tension (st) (Hansch and Fujita, 1964), wiener index (W), mean wiener index (W_A), molecular weight (MW) (Hansch and Fujita, 1964) and molecular connectivity ($^0\chi$, $^1\chi$, $^2\chi$) and have been used to study the relationship between parameters and properties. St and mw were calculated by ACD Lab Chem. Sketch Software version 12 (ACD/ChemSketch 10 (2006); www.acdlabs.com) whereas W, W_A, $^0\chi$, $^1\chi$, $^2\chi$ were evaluated by E-Dragon Software (www.vcclab.org/). The multiple regressions used to derive the correlation were executed with the SPSS 7.5 version program.

2.2. Parameters used

2.2.1. Molecular connectivity index

The first order connectivity index $\chi^{(G)}$ of a graph G is defined by Randic (1975) as follows:

$$\chi = \chi^{(G)} = \sum_{jk} [\delta_j \delta_k]^{-0.5}$$

where δ_j and δ_k are the valences of vertices j and k that are equal to the number of bonds connected to the atoms j and k, in G. In the case of hetero-systems the connectivity is given in terms of valence delta values δ_j and δ_k of atoms j and k and is denoted by χ^r. This version of the connectivity index is called the valence connectivity index and is defined as follows:

$$X^r = \chi^{r(G)} = \sum_{jk} [\delta_j^r \delta_k^r]^{-0.5}$$

where, the sum of all bonds j and k of the molecule is taken. Valence delta values are given by the following expression:

$$\Delta_j^v = \frac{Z_j^v - H_j}{Z_j - Z_k - 1}$$

where Z_j is the atomic number of atom j, Z_j^v is the number of valence electrons of the atom j and H_j is the number of hydrogen atoms attached to atom j. The Δ_j^v values are available in the book written by Kier and Hall (1976).

2.2.2. Indicator parameters

Indicator variables or parameters, sometimes called dummy variables or de novo constants (Recantint et al., 1986) are used in linear multiple regression analysis to account for certain features which cannot be described by continuous variables. In QSAR equations, they normally describe a certain structural element, be it a substituent or another molecular fragment. Thus, Free Wilson analysis may be interpreted as a regression analysis approach using only indicator variables.

2.2.3. Molecular weight (MW)

Molecular weight descriptor has been used as the descriptor in systems such as transport studies where diffusion is the mode of operation. It is an important variable in QSAR studies pertaining to cross-resistance of various drugs in multi-drug resistant cell lines

2.2.4. Wiener index (W)

Wiener index (W) is a widely and oldest used topological index. It is based on the vertex-distances of the respective molecular graph. The Wiener index (W) was proposed in 1947 by Wiener and it is defined as the sum of overall bonds of the product of the number of vertices on each side of the bond. Let us denote a molecular graph G and v_1, v_2, v_3,...,v_n its vertices. Let $d(v_j; v_k/G)$ stand for the distance between the vertices v_{ij} and v_k. Then the Wiener (1947) index is defined as:

$$W = W(G) = 1/2 \sum_j^n \sum_k^n d(v_j, v_k|G)$$